

AUG 01 2005
BEST AVAILABLE COPYI. AMENDMENTS TO THE SPECIFICATION*Page 2, lines 5 to 15:*

A known medicament that contains a sulfinyl group is modafinil Modafinil, i.e. 2-[(diphenylmethyl)sulfinyl]acetamide. According to various synthetic methods, intermediate 2-[(diphenylmethyl)thio]acetic acid or 2-[(diphenylmethyl)thio]acetamide is oxidized with hydrogen peroxide to give 2-[(diphenylmethyl)sulfinyl]acetic acid, or 2-[(diphenylmethyl)sulfinyl]acetamide, respectively. This oxidation, usually performed with 110 volumes hydrogen peroxide, involves safety problems. Similar problems also occur in the synthesis of other biologically active sulfinyl compounds, such as sulindac Sulindac, i.e. (Z)-5-fluoro-2-methyl-1-[[4-(methyl-sulfinyl)phenyl]methylene]-1H-indene-3-acetic acid, and the so-called "prazoles", i.e. [[[pyridyl)methyl]sulfinyl]benzimidazole derivatives, which are known anti-secretory agents.

Page 3, lines 10 to 25:

The process of the invention is particularly useful for the preparation of biologically active compounds containing sulfinyl or sulfonyl groups, such as modafinil Modafinil; modafinil-sulfone Modafinil-sulfone (i.e. modafinil-sulfone Modafinil-sulfone analogue); sulindac Sulindac; sulindac-sulfone Sulindac-sulfone (i.e. sulindac sulfone Sulindac-sulfone analogue); dapsone Dapsone; and [[[pyridyl)methyl]sulfinyl]benzimidazole derivatives, known as anti-secretory agents, such as those disclosed in WO 01/04109 and EP 998944, in particular:

omeprazole Omeprazole, i.e. 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole;

pantoprazole Pantoprazole, i.e. 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole;

lansoprazole Lansoprazole, i.e. 2-[[[methyl]4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole;

timoprazole Timoprazole, i.e. 2-[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole);

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picoprazole Picoprazole, i.e. 5-ethoxycarbonyl-6-methyl-2-[(3-methyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole;

rabeprazole Rabeprazole, i.e. 2-[[3-methyl-4-(3-methoxypropoxy)-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole;

exomeprazole Exomeprazole, i.e. the (S)-isomer of omeprazole Ormeprazole.

Page 4, lines 1 to 9:

- intermediates for the preparation of sulindac Sulindac, in particular those disclosed in U.S. Pat. No. 3,647,858, such as 1-(4-fluorophenyl)-2-(4-methylthio-phenyl)-ethanone and (Z)-5-fluoro-2-methyl-1-[[4-(methylthio)-phenyl]methylene]-1H-indene-3-acetic acid; preferably (Z)-5-fluoro-2-methyl-1-[[4-(methylthio)-phenyl]methylene]-1H-indene-3-acetic acid;
- intermediates for the preparation of modafinil Modafinil, such as 2-[(diphenylmethyl)thio]acetic acid and 2-[(diphenylmethyl)thio]acetamide;
- intermediates for the preparation of dapsone Dapsone, such as 4,4'-thiobisbenzenamine;

Page 5, lines 4 to 7:

Examples of intermediate compounds containing a sulfinyl group are sulindac Sulindac, modafinil Modafinil, 1-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-ethanone, and 2-[(diphenylmethyl)sulfinyl]acetic acid.

Page 7, lines 10 to 12:

Preparation of (5-difluoromethoxy)-2-[(4-chloro-3-methoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (Intermediate for the Preparation of pantoprazole Pantoprazole)

Page 8, line 17 to page 9, line 2:

Using the same procedure, the following compounds can be prepared:
omeprazole Ormeprazole from 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole;

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pantoprazole Pantoprazole from 5-difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio-1H-benzimidazole;
lansoprazole Lansoprazole from 2-[[[methyl]-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole;
omeprazole Timoprazole from 2-[[[2-pyridinyl)methyl]thio]-1H-benzimidazole;
piceprazole Picoprazole from 5-ethoxycarbonyl-6-methyl-2[[[3-methyl-2-pyridinyl)methyl]thio]-1H-benzimidazole;
rabeprazole Rabeprazole from 2-[[[3-methyl-4-(3-methoxypropoxy)-2-pyridinyl)methyl]thio]-1H-benzimidazole; and
exomeprazole Exomeprazole from (S)-5-methoxy-2[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole.

Page 9, lines 4 to 5:

Preparation of (Z)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetic acid (sulindac Sulindac)

Page 9, lines 6 to 13:

(Z)-5-fluoro-2-methyl-1-[[4-(methylthio)-phenyl]methylene]-1H-indene-3-acetic acid (5 g, 14.7 mmoles) is dissolved in dichloromethane (25 ml). The solution is added with 5.4 g (14.26 mmoles) of 73% w/w phthalimidoperhexanoic acid, keeping the temperature at about 20°C. After 18 h, the solution is concentrated to a residue that is crystallized from 15 ml methanol. After drying, 4.8 g of (Z)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetic acid (sulindac Sulindac) is obtained. Molar yield: 91%.

Page 9, line 25 to page 10, line 4:

Preparation of sulindac Sulindac

(Z)-5-fluoro-2-methyl-1-[[4-(methylthio)-phenyl]methylene]-1H-indene-3-acetic acid (5 g, 14.7 mmoles) is dissolved in methanol (40 ml). The solution is added with 5.4 g (14.26 mmoles) of 73% w/w ϵ -phthalimidoperhexanoic acid, keeping the temperature at about 20°C. After 18 h, the solution is concentrated to 15 ml and cooled to 5°C. The

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precipitate is filtered and dried. 4.6 g of (Z)-5-fluoro-2-methyl-1-[(4-(methylsulfinyl)phenyl)methylene]-1H-indene-3-acetic acid (sulindac Sulindac) is obtained.

Page 10, lines 13 to 15:

2-[(diphenylmethyl)sulfonyl]acetic acid from 2-[(diphenylmethyl)sulfinyl]acetic acid; and 2-[(diphenylmethyl)sulfonyl]acetamide (modafinil-sulfone Modafinil-sulfone) from 2-[(diphenylmethyl)sulfinyl]acetamide.

Page 10, lines 17 to 23:

Preparation of modafinil Modafinil

10 g (38.9 mmoles) of 2-[(diphenylmethyl)thio]acetamide are dissolved in 100 ml of dichloromethane. The solution is added with 15.7 g of 68% w/w ε-phthalimidoperhexanoic acid, keeping the temperature at about 20°C, and after 6 h is diluted with water, adjusting the pH to 8-9 with aqueous ammonia. The resulting phases are separated and the organic one is evaporated to dryness, to obtain 8.5 g of 2-[(diphenylmethyl)sulfinyl]acetamide (modafinil Modafinil). Molar yield: 80%.

Page 11, lines 4 to 10:

Preparation of modafinil-sulfone Modafinil-sulfone

10 g (38.9 mmoles) of 2-[(diphenylmethyl)thio]acetamide are dissolved in 100 ml of dichloromethane. The solution is added with 31.4 g of 68% w/w ε-phthalimidoperhexanoic acid, keeping the temperature at 20°C and after 6 h is diluted with water, adjusting the pH to 8-9 with aqueous ammonia. The resulting phases are separated and the organic one is evaporated, to obtain 8.1 g of 2-[(diphenylmethyl)sulfonyl]acetamide (modafinil-sulfone Modafinil-sulfone).

Page 11, lines 16 to 23:

Using the same procedure, the following compounds can be prepared:
2-[(diphenylmethyl)sulfonyl]acetic acid from 2-[(diphenylmethyl)thio]acetic acid;
1-(4-fluorophenyl)-2-(4-methylsulfonyl-phenyl)-ethanone from 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-ethanone; (Z)-5-fluoro-2-methyl-1-[(4-(methylsulfonyl)-

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phenyl]methylene]-1H-indene-3-acetic acid from (Z)-5-fluoro-2-methyl-1-[[4-(methylthio)-phenyl]methylene]-1H-indene-3-acetic acid; and 4,4'-sulfonylbenzenamine (dapsone) from 4,4'-thiobisbenzenamine.

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